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tert-AMINO EFFECT: THE METH-COHN AND REINHOUDT REACTIONS (REVIEW)

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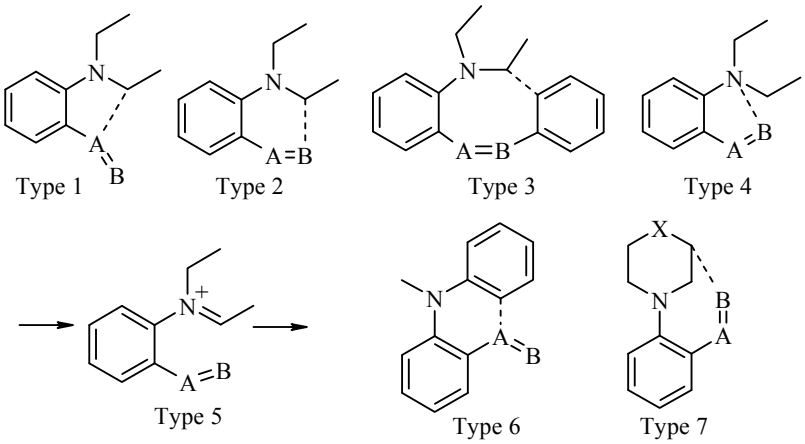
The data published over the last 15-20 years on reactions taking place by the tert-amino effect mechanism have been reviewed.

Keywords: nitrogen-containing heterocycles, spiro heterocycles, *tert*-amino effect, cyclization.

The term "*tert*-amino effect" was proposed in 1972 [1] for the cyclization reactions of tertiary anilines containing various double bonds at the *ortho* position. Meth-Cohn and Suschitzky [1] referred to the first observation of the *tert*-amino effect by Pinnow in 1895 [2]. Many different examples of reactions involving the *tert*-amino effect have now accumulated, and it clearly is a convenient method for the synthesis of an impressive number of nitrogen-containing heterocycles that otherwise might be difficult to obtain. Reviews were published by Reinhoudt in 1990 [3] and by Meth-Cohn in 1996 [4] on heterocyclization reactions that take place by the mechanism of the *tert*-amino effect. Another review dedicated to 1,6- and 1,8-naphthiridine derivatives was published in 2003 by Quintela [5]. In the review [6] that we published in 2005, attention was focused on the use of such reactions for the synthesis of spiro compounds. In the review [7], published in 2006, the cyclization reactions of *ortho*-vinylanilines and their heterocyclic aza analogs were considered, and classification according to the method of ring formation was proposed.



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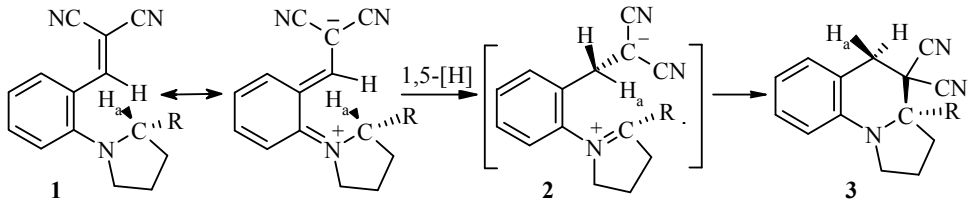
The term "*tert*-amino effect" is generally used to describe the cyclization of conjugated *N*,*N*-disubstituted amines, where the key stage is hydrogen transfer from an unactivated α-carbon atom of an amino group to one of the atoms of a double bond.

It is worth noting that various names have been used for this reaction in the literature: reactions occurring by the *tert*-amino effect mechanism; intramolecular redox process; 1,5(1,7)-hydride shift; reactions at unactivated α-carbon atom; the "Twente variant" of the *tert*-amino effect; redox-neutral C–H bond functionalization; T-reactions; redox/1,5-hydride shift/cyclization; asymmetric sp^3 C–H functionalization, etc. In our opinion the traditional nomenclature (named reactions) should be used: cyclization of *N*,*N*-disubstituted anilines (heterocyclic amines) that contain unsaturated *ortho*-substituents with at least one heteroatom (nitroso, nitro, azo, azomethino, amino, or carbonyl groups) is the *Meth-Cohn reaction* [1,4]; reaction of amino derivatives with an *ortho*-vinyl group leading to the formation of a new carbon–carbon bond is the *Reinhoudt reaction* [3].

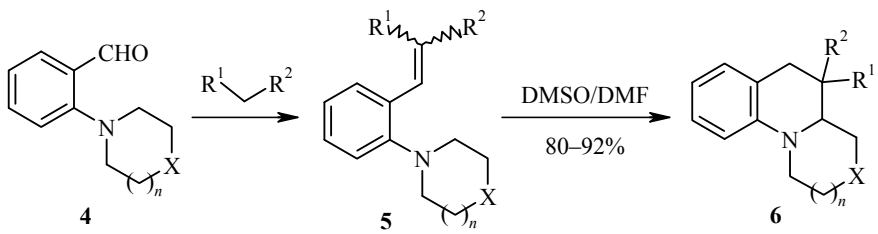
In this review we consider examples of the Meth-Cohn and Reinhoudt reactions published over the last 15-20 years. Special attention is paid to the formation of carbon–carbon bonds.

Reinhoudt Reaction

The first example of such a reaction is the rapid thermal cyclization of tertiary anilines containing a dicyanovinyl group at the *ortho* position, which is a reaction of type 2 by this classification [8]. The cyclization mechanism proposed by Reinhoudt's group is based on kinetic investigations and on the use of a deuterium label [9]. It is illustrated for the case of [2-(pyrrolidin-1-yl)benzylidene]malonodinitriles **1** and was presented in a review [3].



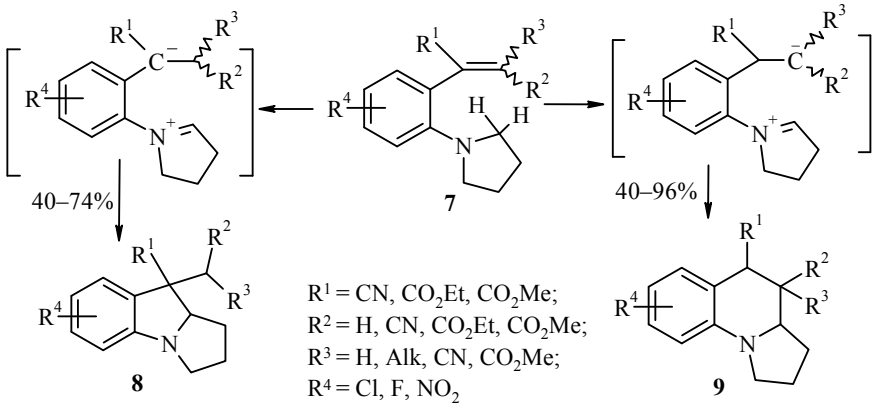
The controlling stage includes the migration of hydrogen in a conformation, in which the vinyl group is separated from the amino group, and leads to a dipolar intermediate **2**. The migrating hydrogen atom (H_a) stays on the same side of the molecule. Subsequently, rotation occurs about the σ-bond with the phenyl substituent, and a new σ-bond is formed between the two oppositely charged carbon atoms, leading to a new six-membered ring **3**. It was shown that a C–C bond is formed from the side of the leaving proton H_a, i.e., the configuration at the asymmetric α-carbon atom of the dialkylamino group is preserved. During examination of the first stage mechanism, both [1,5]-sigmatropic (a synchronous process) and 1,5-hydride (a two-stage process) shifts were discussed. The stereochemical features of this rearrangement, including enantio- and diastereoselectivity, can be reconciled well both with a sigmatropic and with an ionic mechanism of migration.



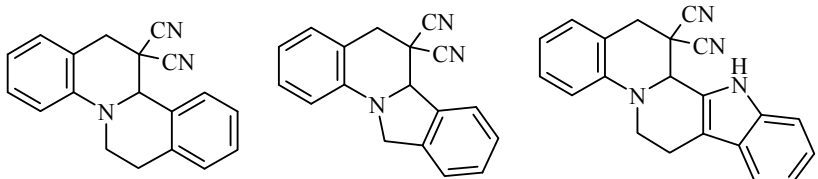
R^1, R^2 = CN, CO_2Me, CO_2Et; X = CH_2, *n* = 0, 1, 2; X = O, *n* = 1

The effect of the structure of the amino group and the vinyl substituent on the cyclization has been well studied and described for the benzaldehyde derivatives **4**. It was shown that the vinyl derivatives **5** underwent cyclization to quinolines **6** not only thermally [10], but also under microwave treatment [11] and electron impact [12].

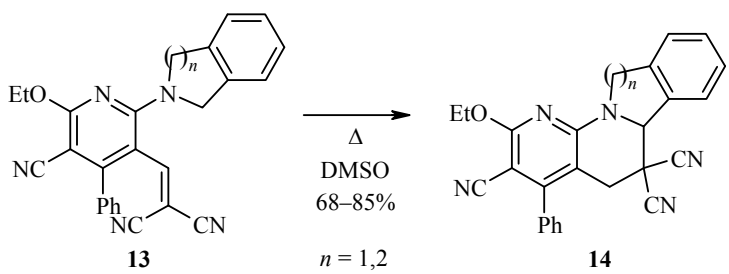
Professor Reinhoudt's group established the criteria for the occurrence of a type 2 cyclization (see p. 357). A systematic study of the effect of substituents in the *ortho*-vinyl group of dialkylanilines **7** [13-15] showed that cyclization in the case of an electron-withdrawing group at the α-position of the vinyl function (R^1) led to the formation of five-membered rings **8** (a type 1 cyclization). Compounds having two electron-withdrawing groups at the β-position of the vinyl function (R^2 and R^3) formed six-membered rings **9** (a type 2 cyclization). If there was only one electron-withdrawing group at the β-position of the vinyl group (R^2 = H), the reaction did not occur.



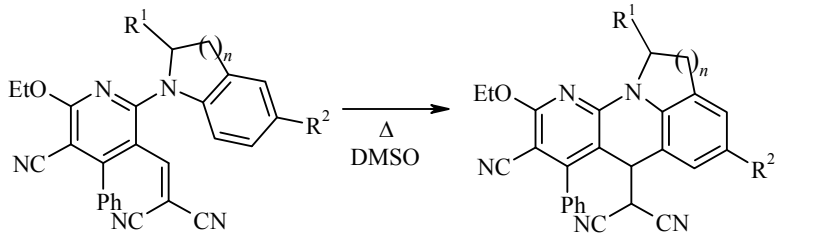
The synthesis of isoquinolino[2,1-*a*]quinoline **10**, isoindolo[2,1-*a*]quinoline **11**, and indolo[2',3':3,4]pyrido[1,2-*a*]quinoline **12** (in 70-90% yields) was similar to the synthesis of compound **5** with the exception that simple amines were replaced by more complicated ones, such as 1,2,3,4-tetrahydroisoquinoline, 2,3-dihydro-1*H*-isoindole, and 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole. Reactions in which secondary amines of natural origin [16] and chiral bicyclic amines [17] were used have also been described.



It is not only tertiary anilines with an *ortho*-vinyl group that can be cyclized by the mechanism of the *tert*-amino effect. The cyclizations of tertiary amines of pyridine **13** have been described [18, 19]. We consider it necessary to mention two unexpected paths of ring closure that emphasize the important role of the tertiary amino group in cyclization by the mechanism of the *tert*-amino effect.



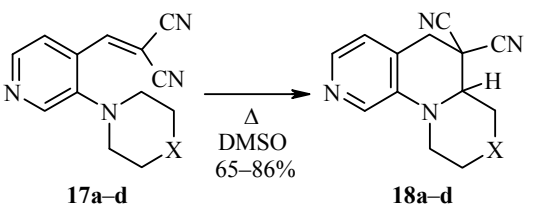
The first example represents the anomalous reactions observed with the indoles and quinolines **15a-d** [18]. Compounds **13** and **15a-d** underwent cyclization in different ways. It was found that upon thermal cyclization of the pyridines **13** the reaction followed exclusively the *tert*-amino effect mechanism; the corresponding tetracyclic compounds **14** were isolated, whereas the pyridines **15a-d** containing a less basic nitrogen atom in the amino group [18] gave the conjugated cyclic systems **16a-d** by successive electrocyclization–aromatization.



15a–d **16 a** (82%), **b** (80%), **c** (63%), **d** (72%)

a *n* = 1, $R^1 = R^2 = H$; **b** *n* = 2, $R^1 = R^2 = H$; **c** *n* = 1, R^1 = Me, $R^2 = H$; **d** *n* = 2, R^1 = Me, R^2 = F

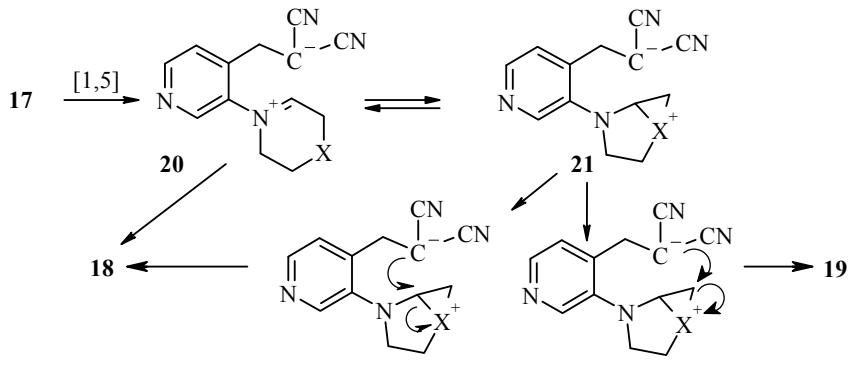
The second example describes ring closure in the 4-amino-3-vinylpyridine derivatives **17**, obtained from 3-bromopyridine-4-carbaldehyde [19]. It was shown that cyclization of the piperidine derivative **17a** led to the expected product **18a**. However, heating of the 4-piperazino-, 4-morpholino-, or 4-thiomorpholino-3-vinyl pyridine derivatives **17b-d** in DMSO solution led to a product mixture containing not only the pyridopyridines **18b-d** but also the tricyclic azepines **19b-d**.



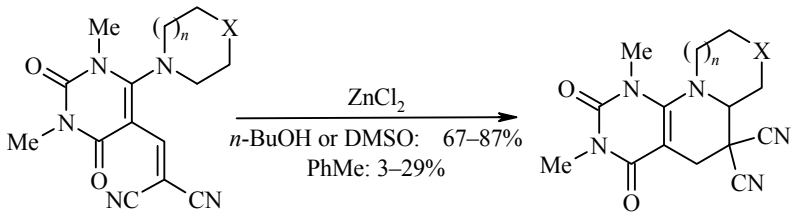
17a–d **18a–d** **19b–d**

	X	**18** : **19**
a	CH_2	1 : 0
b	NPh	1 : 2
c	O	1 : 1.2
d	S	1 : 1.6

The formation of the products **19b-d** was explained by the presence of the intermediate **20**, which was formed by a 1,5-sigmatropic shift from the vinyl derivative **17**. Cyclization of compounds **17** could lead to the tetrahydropyridines **18** through the formation of the imine **20**. If there was a heteroatom (X = N, O, S) in the cycloalkylamine, then generation of the isomeric structure **21** was possible, where cyclization could lead both to the six-membered heterocycles **18** and to the azepines **19.**



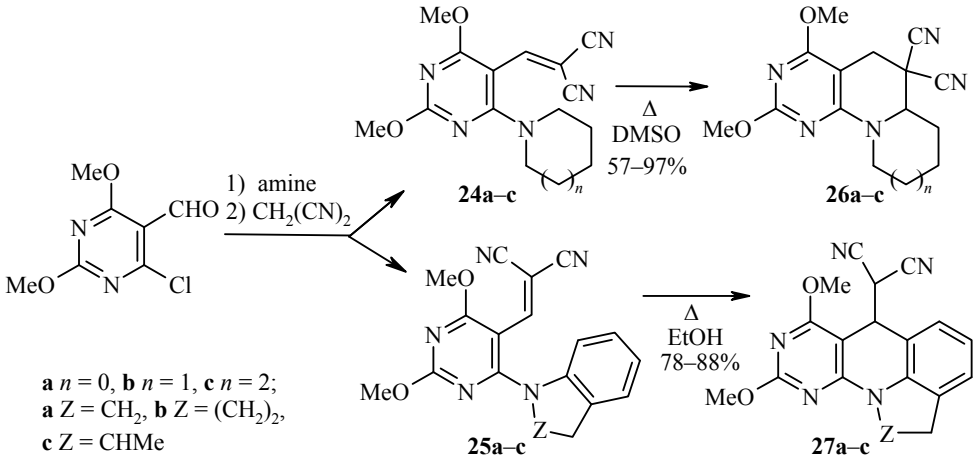
Thermal cyclization by the *tert*-amino effect mechanism was also typical for the diazine derivatives **22a-e**. Like the previously mentioned *ortho*-vinylanilines **5** and *ortho*-vinylpyridylamines **17,** the 6-amino-5-vinyluracil derivatives **22a-e** underwent cyclization when heated in toluene in the presence of $ZnCl_2$; the pyrido[2,3-*d*]pyrimidines **23a-e** were formed as a result. The yields were usually very low under these conditions (3-29%), while the pyrrolidine derivatives **22a** hardly reacted at all [20]. However, under different reaction conditions, in refluxing *n*-butanol [21] or DMSO at 140°C, cyclization of some of these uracil derivatives **22a-e** gave higher yields (67-87%).



22a–e **23a–e**

a *n* = 0, **b–e** *n* = 1; **a, b** X = CH_2, **c** X = O, **d** X = CHBn, **e** X = CHMe

During the cyclization of aromatic derivatives of pyrimidines **24** and **25a-c**, which have *tert*-amino- and dicyanovinyl groups at neighboring positions, two types of cyclic systems were formed depending on the structure of the *tert*-amino group. From compounds **24a-c**, containing an alicyclic *tert*-amino group, the tricyclic products **26a-c** were formed by the the *tert*-amino effect mechanism. The alkenes **25a-c**, in which the the amino group nitrogen belonged to an indole or quinoline, were transformed into the tetracycles **27a-c**, the formation of which can include electrocyclization, similar to the pyridine analog **16** formation from the olefin **15** [22].

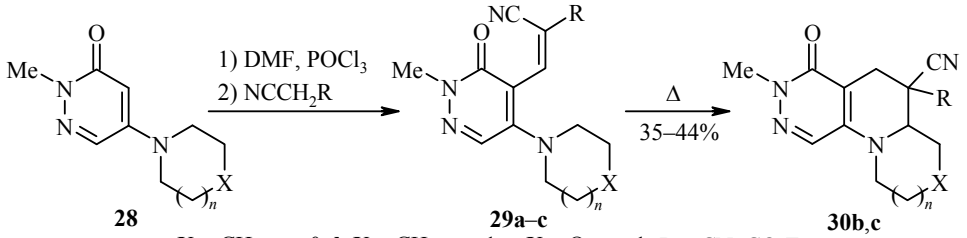


a *n* = 0, **b** *n* = 1, **c** *n* = 2;
a Z = CH_2, **b** Z = $(CH_2)_2$,
c Z = CHMe

24a–c **26a–c** **25a–c** **27a–c**

The first report on using the *tert*-amino effect for the synthesis of conjugated cyclic pyridazine systems appeared more than 15 years ago [23]. The synthesis was based on the cyclization of pyridazin-3(2*H*)-ones **29a-c** containing vinyl and *tert*-amino groups, which were obtained in two stages from 5-dialkylaminopyridazinones **28**. The prolonged heating of compounds **29b**,**c** in DMSO at 150°C (39-44 h) led to the formation of tricyclic compounds **30b**,**c** with yields of 35-44%. Cyclization of compound **29a** did not occur in refluxing butanol [24].

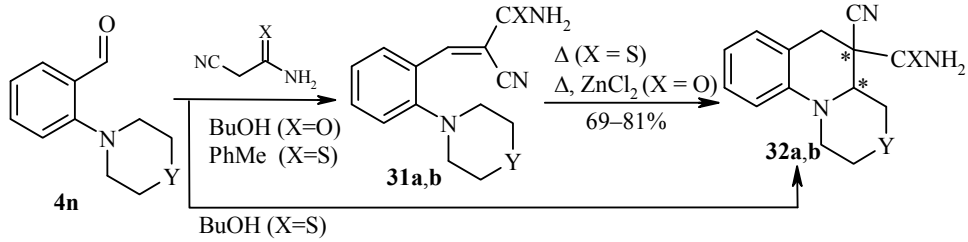
All the aforementioned cyclization examples assume that strong electron acceptors at the terminal carbon atom of the vinyl group are required for cyclization. Indeed, two cyano groups can be considered the optimal substituents for ring closure, as was demonstrated for the case of the relatively unreactive heterocyclic analogs of tertiary anilines.



28 **29a–c** **30b,c**

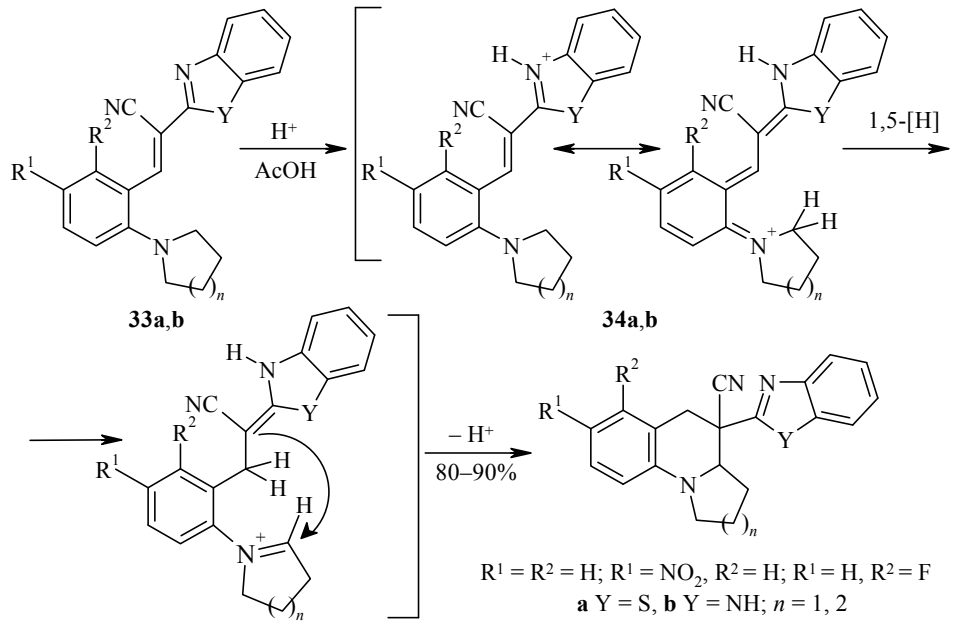
a X = CH_2, *n* = 0; **b** X = CH_2, *n* = 1; **c** X = O, *n* = 1; R = CN, CO_2Et

Most of the cyclization substrates had two cyano or ester groups at the terminal carbon atom of the vinyl group. The cyclization reactions of compounds with two different substituents at the β-carbon atom of the vinyl group have been studied to a much lesser degree. We showed [25] that the cyclization of thioamide **31b** led to the (4a*R**,5*R**)-isomer **32b**, whereas the amide **31a** did not undergo cyclization under such conditions. It should be noted that compound **32b** contains two asymmetric centers, and the formation of two diastereomers is therefore possible. It was shown that the reaction was stereoselective and formation of one diastereomer was favored (*de* 95-98%). It should be noted that the reaction of the benzaldehyde **4n** with cyanothioacetamide in butanol occurred in one stage, forming the tricyclic compound **32b**. The cyclization of the amides **31a** required a Lewis acid catalyst ($ZnCl_2$) [26].



4n **31a,b** **32a,b**

Y= NC_6H_4OMe-4; **a** X = O, **b** X = S



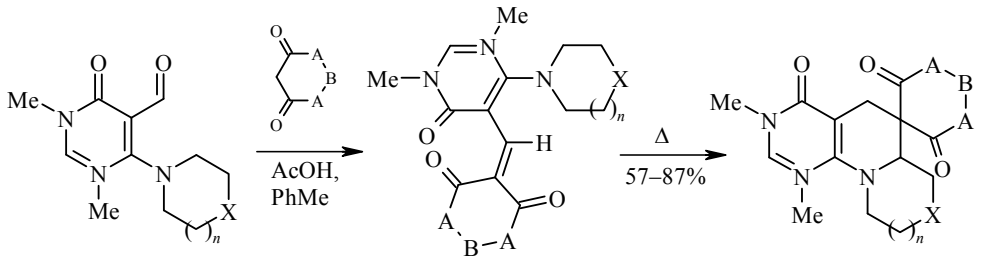
33a,b **34a,b**

$R^1 = R^2 = H$; $R^1 = NO_2$, $R^2 = H$; $R^1 = H$, $R^2 = F$

a Y = S, **b** Y = NH; *n* = 1, 2

Tverdokhlebov [27] and Ryabukhin [28] studied the cyclization of benzothiazoles **33a** and benzimidazoles **33b**. It was found that the reaction was facilitated by acid catalysis. The authors explained this by protonation at the nitrogen atom of the heterocycle and formation of the structure **34**.

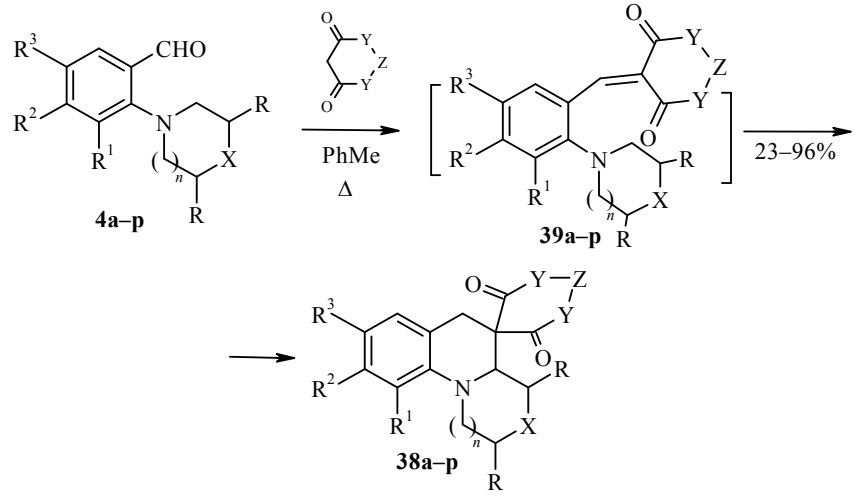
The first example of spiro-coupled heterocycle synthesis by the *tert*-amino effect mechanism was published in 2000 [10]. In spite of the electron-deficient pyrimidine ring, the reaction with cyclic active methylene components was shown to increase the rate of compound **36** cyclization to the spirocyclic systems **37.**



35a–c **36a–c** **37a–c**

a A = NMe, B = C = O, X = O, *n* = 1; **b** A = O, B = $C(CH_3)_2$, X = CH_2, *n* = 0;
c A = B = X = CH_2, *n* = 1

The use of the *tert*-amino effect for the synthesis of new spirocyclic conjugated pyridodiazines [29-31] was quite effective, in that the vinyl derivatives **36a-c** could be easily obtained by Knoevenagel condensation of pyrimidine aldehydes **35a-c** with *N*,*N*-dimethylbarbituric acid or Meldrum's acid. Compounds **36a-c** underwent transformation with remarkable ease, providing access to the corresponding tetrahydropyridines **37a-c** with spirocyclic substituents. In fact, compounds **36a-c** cyclized at a lower temperature and more quickly than the dicyanovinyls **29a-c**.



4a–p **39a–p** **38a–p**

	X	R		X	R		X	R		X	R		X	R
a	O	H	**d**	O	Me	**g**	CH_2	Me	**i**	CHPh	H	**l**	NMe	H	**n**	NC_6H_4OMe-4	H
b	S	H	**e**	$(CH_2)_2$	H	**h**	CH—N	H	**j**	CHMe	H	**m**	NPh	H	**o**	NC_6H_4Cl-3	H
c	CH_2	H	**f**	CH_2	H				**k**	$CHCH_2Ph$	Me				**p**	NCH_2Ph	H

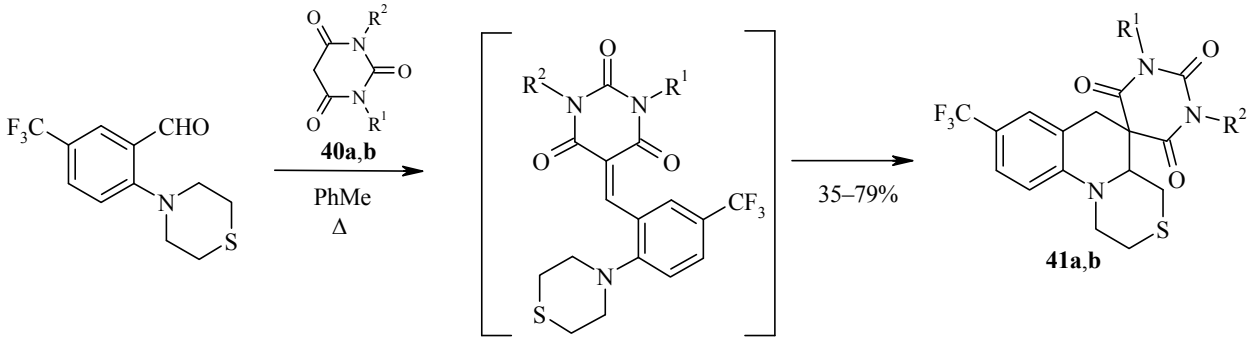
a,**b**,**d**–**p** *n* = 1, **c** *n* = 0
$R^1 = R^3 = H$, R^2 = H, Cl, Br, F; $R^1 = R^2 = H$, R^3 = Br, F, CF_3; R^1 = F, $R^2 = R^3 = H$
X = CO, Y = NMe; X = CMe_2, Y = O; X = Y = CH_2, Y = CMe_2, X = CH_2

On the basis of X-ray structural analysis data [30], the authors concluded that the more sterically hindered starting compounds underwent faster rearrangement, thus cyclization removed the steric strain. A phenyl group at position 6 of the pyridazine ring also increased the cyclization rate of compound **28**. This can be explained by a decrease in the conformational freedom of the neighboring *tert*-amino group, which promoted migration of the hydrogen and facilitated the ring closure.

We showed [32-34] that the reaction of cyclic CH acids with *ortho*-aminobenzaldehydes **4** took place in one stage with the immediate formation of two C–C bonds and led to the spiroheterocycles **38**.

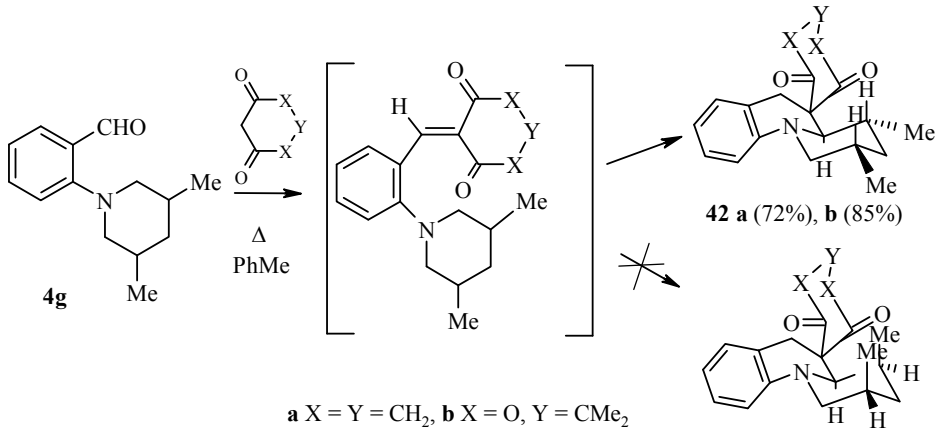
The reaction proceeded similarly in the case of thiobarbituric acid [35-37]. The authors also demonstrated that condensation under mild conditions (aqueous ethanol, 50°C, 5 min [37]) allowed to isolate the intermediate vinyl derivatives **39** with yields up to 86%.

In the case of using the monosubstituted barbituric acids **40a**,**b**, the formation of two isomers was possible. We showed [38] that with the monosubstituted barbituric acid **40b** a 1:1 mixture of spiro-coupled fused [1,2-*a*]quinolines **41b** was formed in 79% yield. One of the isomers could be isolated with a yield of 33% by fractional crystallization from aqueous alcohol.



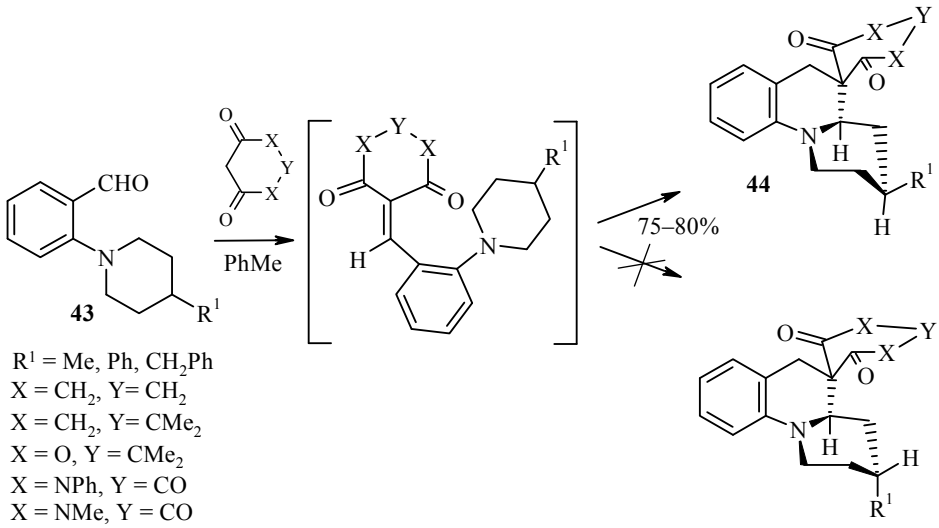
a $R^1 = R^2 = Me$
b $R^1 = H$, $R^2 = C_6H_4CF_3$-4

We also established [39] that the reaction of 2-(3,5-dimethylpiperidino)benzaldehyde (**4g**) with Meldrum's acid and cyclohexanedione was stereoselective and led to the formation of only one isomer **42b** with the axial arrangement of the hydrogen atoms at positions 4 and 4a of the pyrido[1,2-*a*]quinoline ring, as shown by the spin-spin coupling constant J = 9.7-9.8 Hz in the ^{1}H NMR spectra of the obtained compounds. It was thus found that the cyclization by *tert*-amino effect mechanism occurred diastereoselectively when there was a substituent at the β-carbon atom in the dialkylamino group.

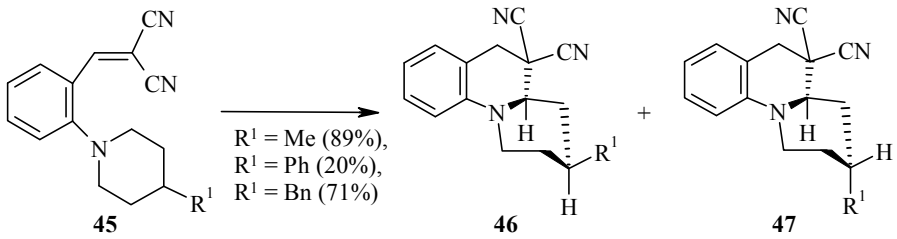


a $X = Y = CH_2$, **b** X = O, $Y = CMe_2$

The 2-(4-*R*-piperidino)benzaldehydes **43** selectively cyclized by *tert*-amino effect mechanism with cyclic activated methylene compounds (Meldrum's acid, 1,3-cyclohexanedione, and *N*,*N*-disubstituted barbituric acids) with the formation of spiro-coupled 2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolines **44** with axially arranged hydrogen atoms at positions 3 and 4a of the benzo[*c*]quinolizine ring [40, 41].

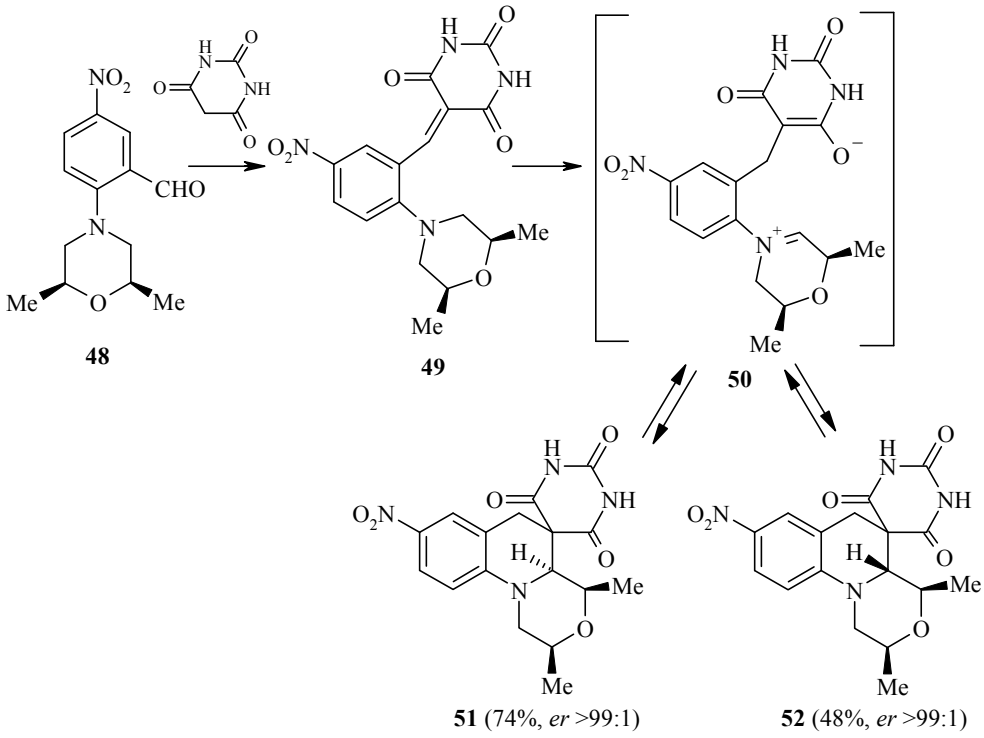


At the same time, the cyclization of the similar derivatives **45** obtained from a noncyclic methylene component (malonodinitrile) led to the formation of two isomeric products **46** and **47** (in a 1:1 ratio) [41].

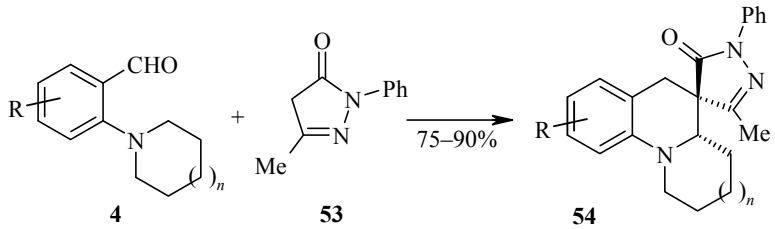


The selective course of the cyclization in the case of aldehydes **43** could be explained by steric factors. During the formation of the intermediate olefin, the double bond was probably turned in such a way that the equatorial proton at the α-carbon atom was close to the double bond. It should be noted that the possibility of a π···H bond in such compounds was demonstrated [37], and this explained the low barrier to hydrogen migration from the α-carbon atom at the amino group to the double bond carbon atom [42]. Here the substituent at position 4 of the piperidine fragment was located equatorially due to the steric influence of the bulky cyclic substituent at the double bond. A similar effect was not observed in the cyclization of compound **45**, allowing the formation of two isomers **46** and **47** [41].

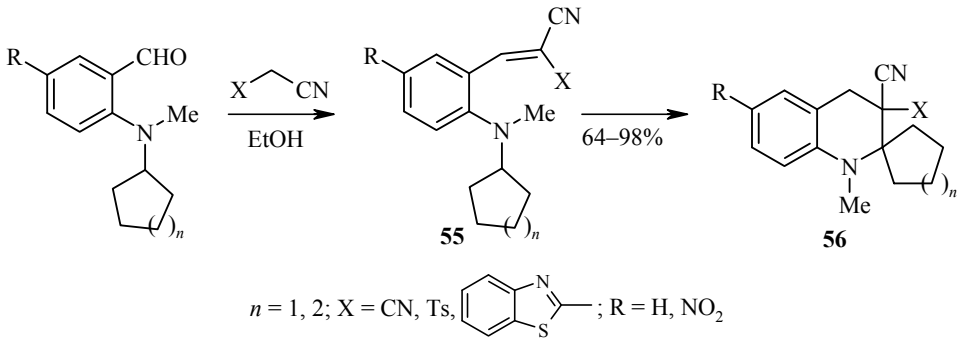
The authors of works [43-46] studied the reaction of the benzaldehyde **48** with barbituric acid by ^{1}H NMR spectroscopy and suggested a stereochemical path for the reaction. The product **49** was readily formed at room temperature. The bipolar intermediate **50** was formed by an intramolecular hydrogen shift. The kinetically controlled product **51** was formed as a result of axial attack by the enolate on the iminium ion. Compound **51** further thermally isomerized by a retro-Mannich reaction to the zwitterion **50**, which underwent cyclization [45] to the thermodynamically favored product **52.**



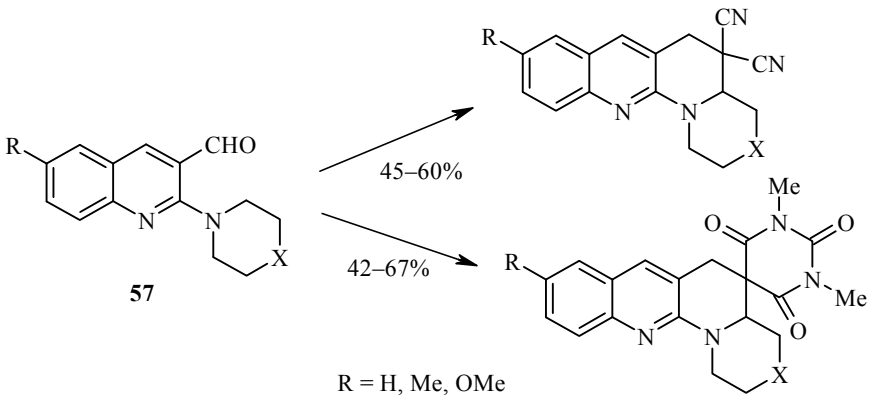
The use of 5-methyl-2-phenylpyrazol-3-one **53** as the active methylene component [28, 47] in the reactions with benzaldehydes **4** led to only one of the two regioisomers of the spiro compounds **54**.



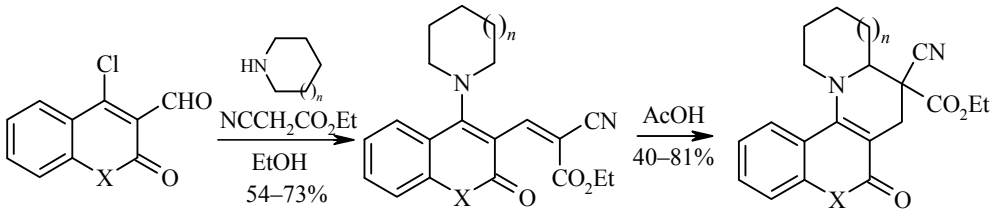
Another approach to the synthesis of the spiro compounds was described by Ukrainian scientists [48]. During the cyclization of compounds **55** containing methyl and cycloalkyl groups at the nitrogen atom, only the spiro compounds **56** were formed.



Cyclization by the *tert*-amino effect of type 2 has also been observed when bicyclic substrates were used; the quinoline derivatives **57** entered readily into the Reinhoudt reaction [49].

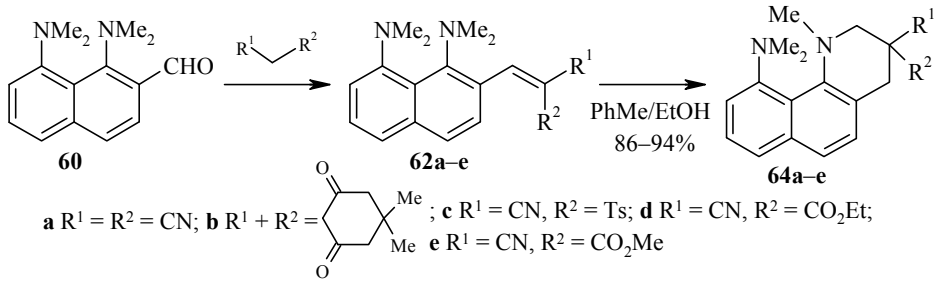


An example of the use of the *tert*-amino effect in coumarin and 2-quinolone systems was described [50]. It should be noted that the Knoevenagel condensation products **58** underwent cyclization to compounds **59** in the presence of acetic acid.

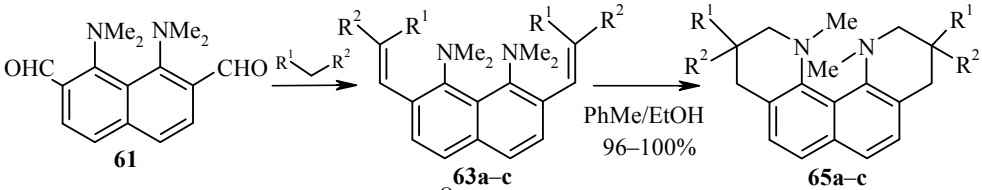


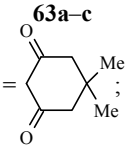
a X = O, *n* = 1; **b** X = O, *n* = 2; **c** X = NMe, *n* = 1

It was shown [51] that compounds **62a-e** and **63a-c**, obtained from 2-formyl- (**60**) and 2,7-diformyl-1,8-bis-(dimethylamino)naphthalenes (**61**), cyclized to 1,2,3,4-tetrahydrobenzo[*h*]quinolines **64a-e** and quino[7,8-*h*]-quinolines **65a-c**, respectively.

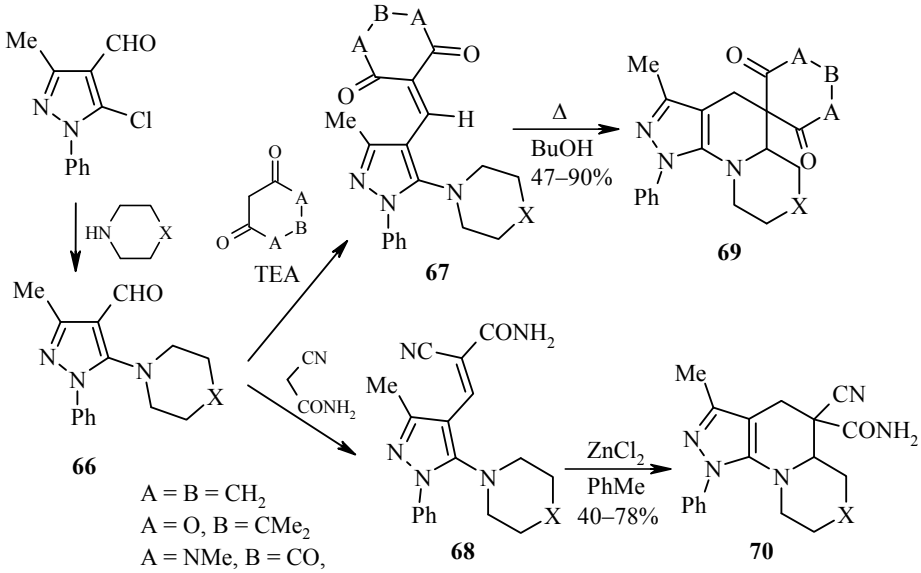


a $R^1 = R^2 = CN$; **b** $R^1 + R^2 =$; **c** $R^1 = CN$, $R^2 = Ts$; **d** $R^1 = CN$, $R^2 = CO_2Et$; **e** $R^1 = CN$, $R^2 = CO_2Me$



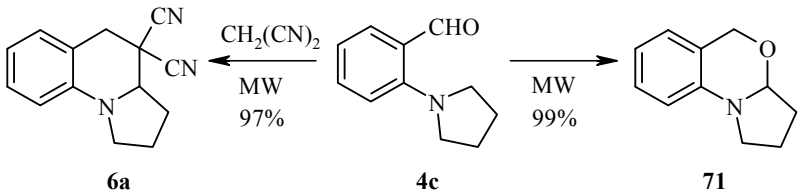
a $R^1 = R^2 = CN$; **b** $R^1 + R^2 =$  ; **c** $R^1 = CN$, $R^2 = CO_2Et$

The Reinhoudt reaction is also characteristic of five-membered heterocycles [6, 26, 28, 30] and their fused analogs [53, 54]. Thus, in 5-chloro-3-methyl-1-phenylpyrazole-4-carbaldehyde [26, 28] the chlorine atom was easily substituted by secondary amines. The tertiary amines **66** thus obtained condensed with acyclic [30, 53] or cyclic [6] active methylene compounds (the vinyl derivatives **67** and **68**) and yielded the condensed systems **69** and **70**.

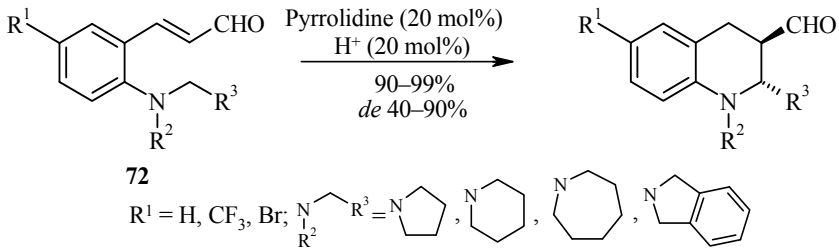


For benzene and pyridazine substrates, ring closure was an exothermic reaction requiring high temperatures. This shows that the method of heat transfer can have particular significance during a thermal cyclization. Accordingly, certain reactions were conducted under the influence of microwave irradiation in order to reduce the reaction time and to prevent or at least reduce the formation of side products [11, 24, 31].

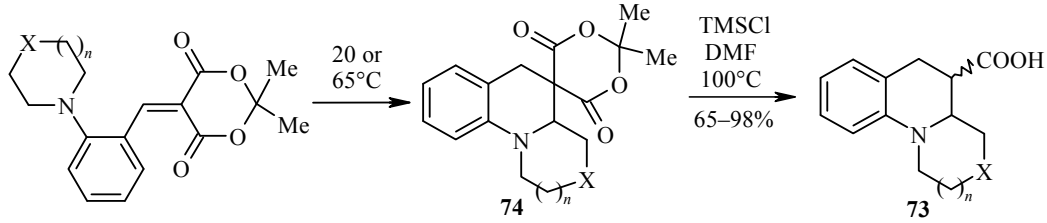
The cyclization of vinyl derivatives of the aldehyde **4c** under microwave irradiation was investigated. Comparing the results of the reactions, conducted under microwave irradiation conditions, and obtained by the traditional method it was established that the reaction time could be reduced significantly with microwave irradiation, even in those cases where cyclization took several days of heating [11]. In their investigations, the authors used water instead of organic solvents. Compound **6a** was synthesized in water medium with a catalytic amount of trifluoroacetic acid in 3 min at 200°C. Cyclization was also achieved by microwave irradiation without a solvent [31]. In the solvent-free syntheses, the yields and purity of the products could be considerably improved. Formation of the oxazine ring **71** was also noted [30]; similar behavior was previously observed during photochemical or thermal reactions in solution phase [55-57].



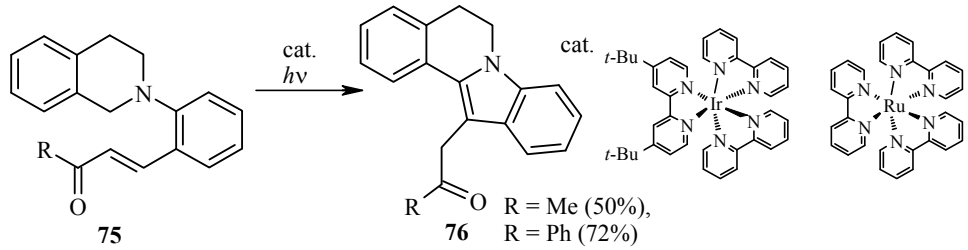
It should be noted that all the above-mentioned reactions took place without a catalyst. However, the use of Lewis acids considerably accelerated [26, 58-61] cyclization by the *tert*-amino effect mechanism and made it possible to extend the applicability of the reaction [26, 61]. It was also shown that using such acids as trifluoroacetic, HCl, HBr or (-)-camphorsulfonic acid allowed to cyclize the vinyl derivatives **72** containing only one withdrawing group at the double bond [57, 62]. It was noted in the review [3] that for cyclization without a catalyst there should be at least two electron-withdrawing substituents in the vinyl group.



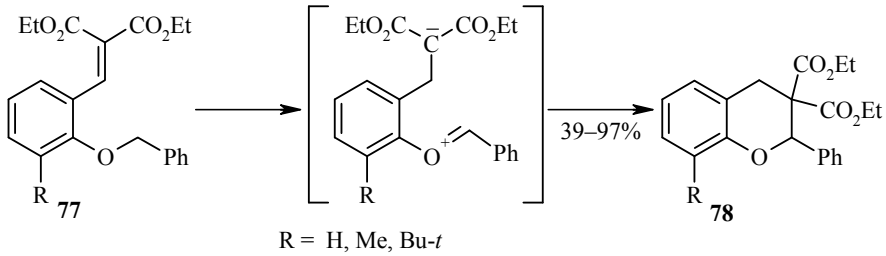
Condensed quinolines **73** containing only one substituent in the ring were obtained by an alternative method, i.e., by hydrolysis and decarboxylation of the Meldrum's acid derivatives **74** [63].



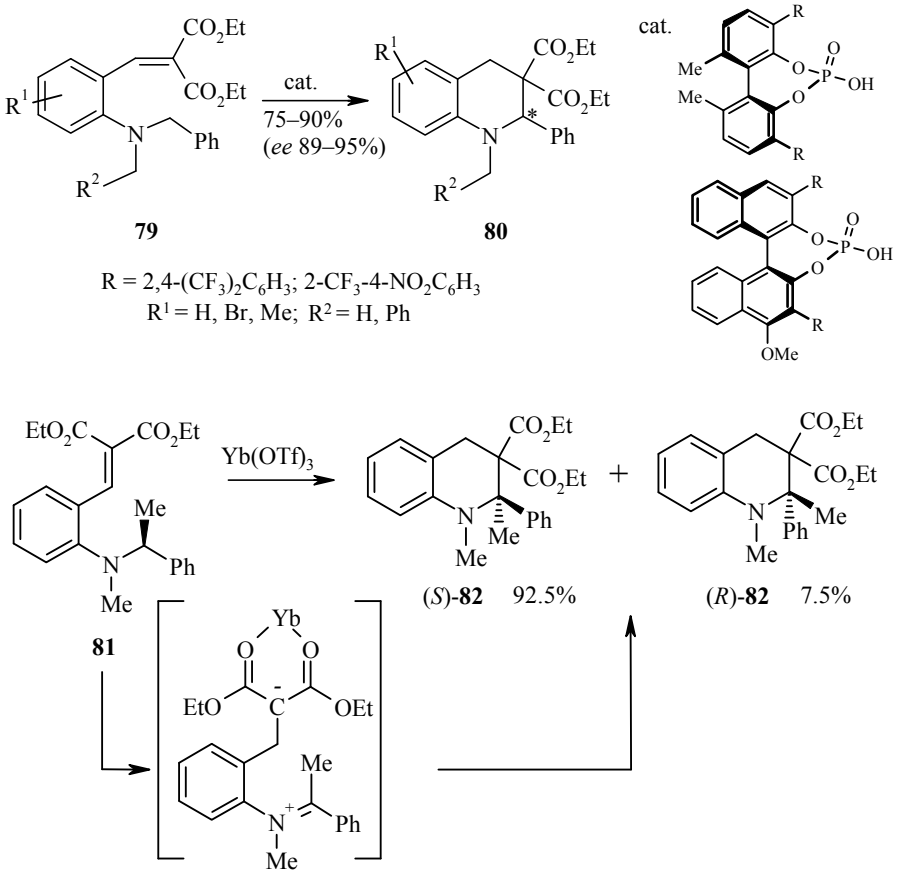
With ruthenium or iridium catalysts [64] it was possible to perform the photocyclization of the chalcone **75** to 5,6-dihydroindolo[2,1-*a*]tetrahydroisoquinoline **76**.



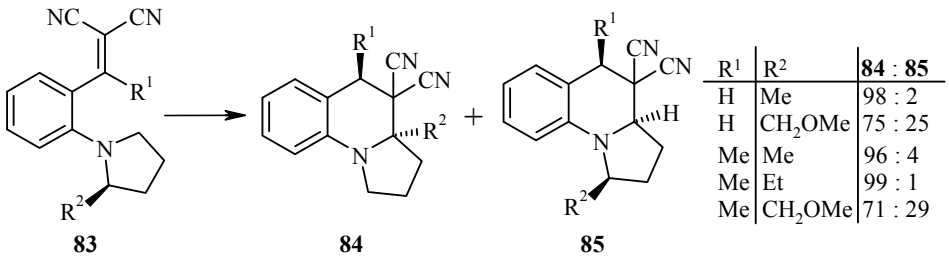
With TsOH or Lewis acids, such as $Sc(OTf)_3$, $TiCl_4$, and $SnCl_4$, it was possible [65, 66] to achieve a similar cyclization of *ortho*-benzyloxybenzylidenemalonates **77,** with the formation of benzofurans **78**.



The use of an optically active catalyst in the cyclization of compounds **79** led to the preparation of one of the enantiomers **80** (*ee* 30-97%) [60, 61]. The use of optically active amines **81** favored the formation of (*S*)-isomer **82** [67].

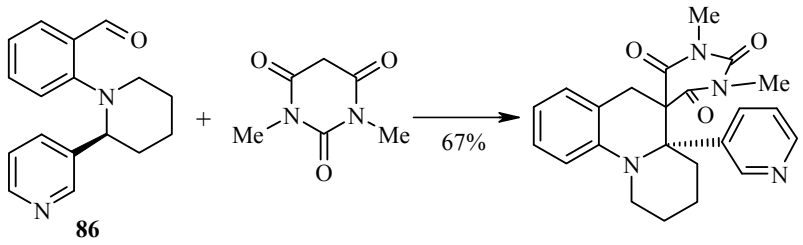


It is important to mention the results described in a remarkable series of papers by Reinhoudt and his colleagues in 1987-1989 [3, 53]. They established that the ring closure could produce regio- and stereoisomers if there was a substituent at the α-position relative to the amino group nitrogen. The dinitrile **83** with R^2 = alkyl and R^1 = H underwent regioselective cyclization, including migration of the hydrogen attached to the carbon atom at which there was an alkyl (methyl or ethyl) substituent, and compound **84** was formed. However, the regioselectivity was significantly lower during the cyclization of α-methoxymethyl-substituted derivatives (R^1 = H and R^2 = CH_2OMe), and both possible regioisomers **84** and **85** were formed as a result. This was explained by the stabilizing effect of the electron-donating alkyl group with respect to the iminium bond formed in the intermediate [53]. The methoxymethyl group, being less electron-donating and sterically more hindered, reduced the regioselectivity.

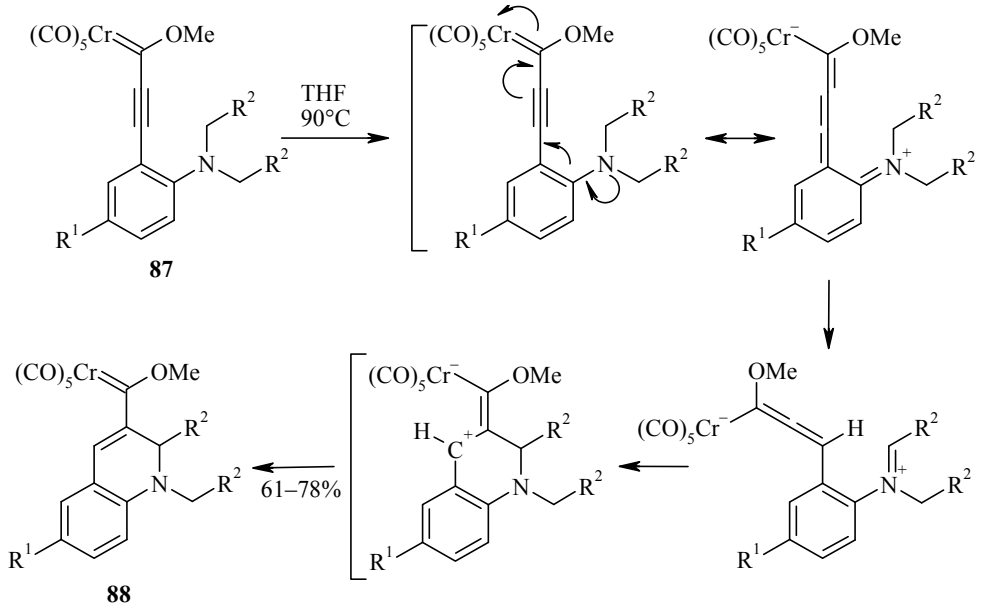


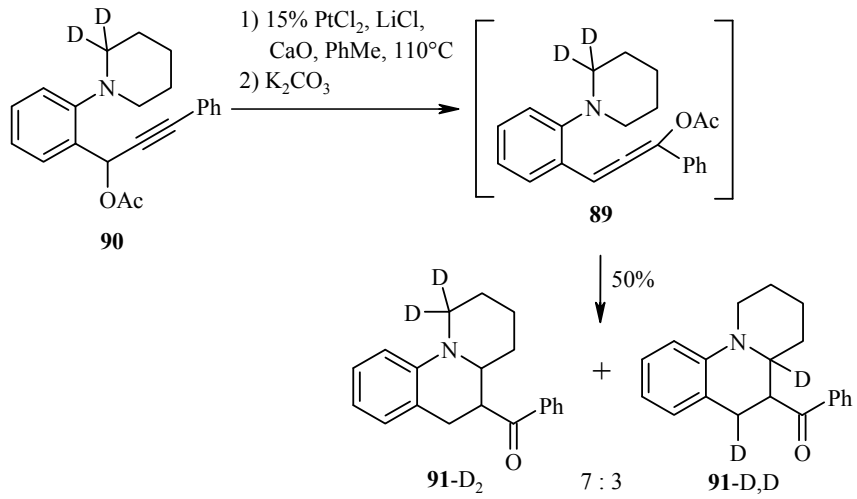
R^1	R^2	**84** : **85**
H	Me	98 : 2
H	CH_2OMe	75 : 25
Me	Me	96 : 4
Me	Et	99 : 1
Me	CH_2OMe	71 : 29

In accordance with the stereochemistry of the reaction, self-reproduction of the chirality was observed during the cyclization of certain chiral substrates, such as the piperidine **86** [17, 68].



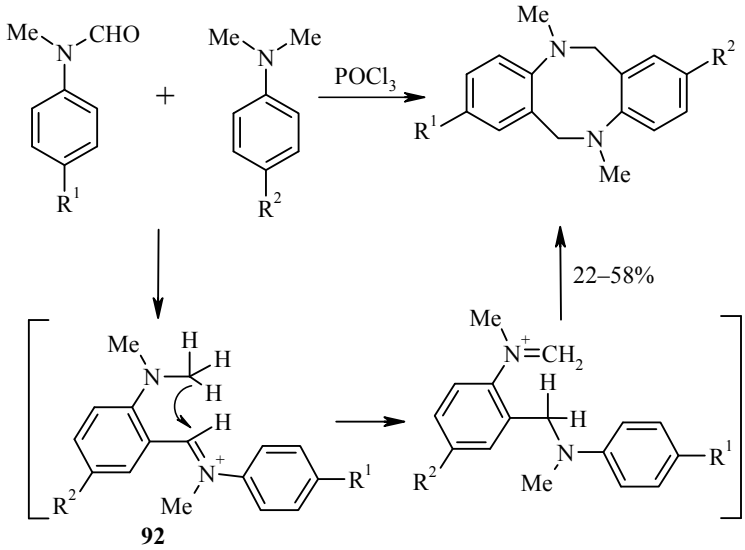
The formation of a C–C bond has not been limited to a vinyl substituent at the *ortho* position relative to the dialkylamino group. Thus, it was demonstrated by Spanish scientists [69, 70] that the acetylene fragment of the carbene complex **87** rearranged on heating to the 1,2-dihydroquinoline fragment of compound **88**. It was shown by quantum-chemical calculations that the rate-limiting step was migration of a hydrogen atom, where the activation energy amounted to 29.6 kcal/mol at 90°C [69]. This value was slightly above the experimentally determined activation energy for the cyclization of *ortho*-vinylanilines **5** at 100°C (24.5 kcal/mol) [37].





Through an experiment with a deuterium-labeled piperidine derivative it was established [71] that the generation of allene **89** from the propargyl ester **90** was accompanied by a 1,3-migration of the acyloxy group, a 1,5-hydride shift, and cyclization to tetrahydroquinolines **91.**

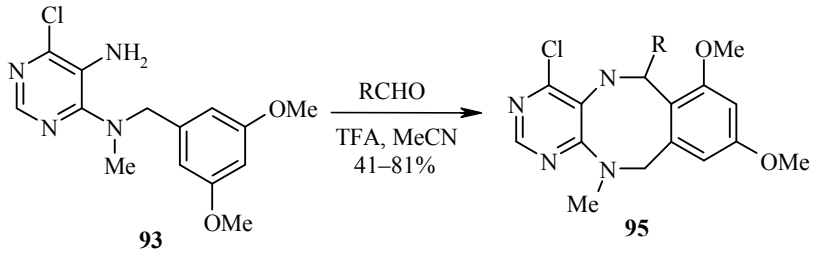
Meth-Cohn [72] noticed that the imines **92** can undergo thermal cyclization of type 3 with the formation of a new C–C bond.



92

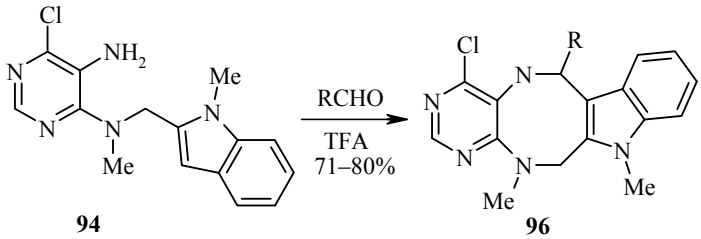
R^1, R^2 = H, OMe, Me, Cl, Br, F

In the case of a benzyl (compound **93**) or methylindole (compound **94**) substituent, the cyclization can take place in a (het)aromatic ring with the formation of pyrimidino[4,5-*c*][2,5]benzodiazocine **95** or indolodiazocine **96** [73]. Such cyclization represents a new variant of the *tert*-amino effect reaction.



93 **95**

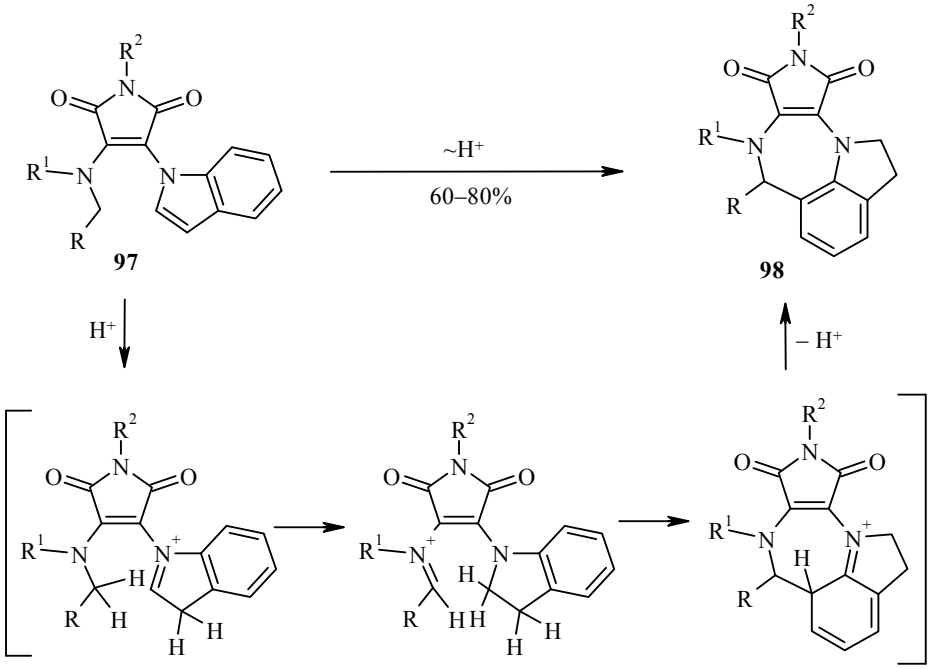
R = *p*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$, *p*-NCC_6H_4, *p*-MeC_6H_4, Bn, *n*-Bu, *n*-Pr, Et



94 **96**

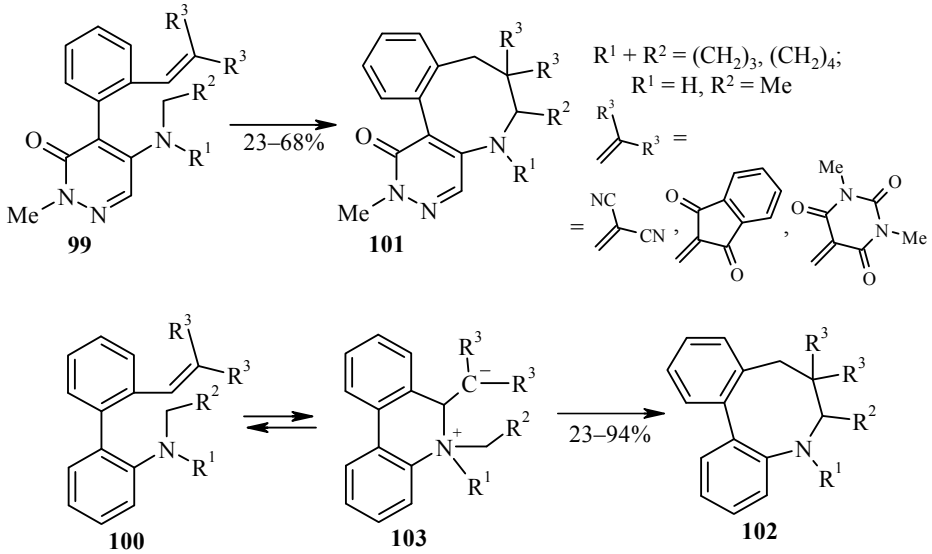
R = *p*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$, *p*-NCC_6H_4, *p*-MeC_6H_4, *n*-Pr, Et, HO_2C

Another example of cyclization involving the α-methylene atom of the amino group was demonstrated by Preobrazhenskaya's group [74, 75]. In the presence of strong acids, 2-(dialkylamino)-3-(indol-1-yl)maleimides **97** underwent cyclization to 1,4-diazepines **98** annelated to an indole ring [75, 76]. Hydride ion transfer was shown [77] to be the rate-limiting step (32.9 kcal/mol) [78]. The intramolecular nature of this hydride transfer was confirmed by an experiment with a deuterated alkylamino group [75].

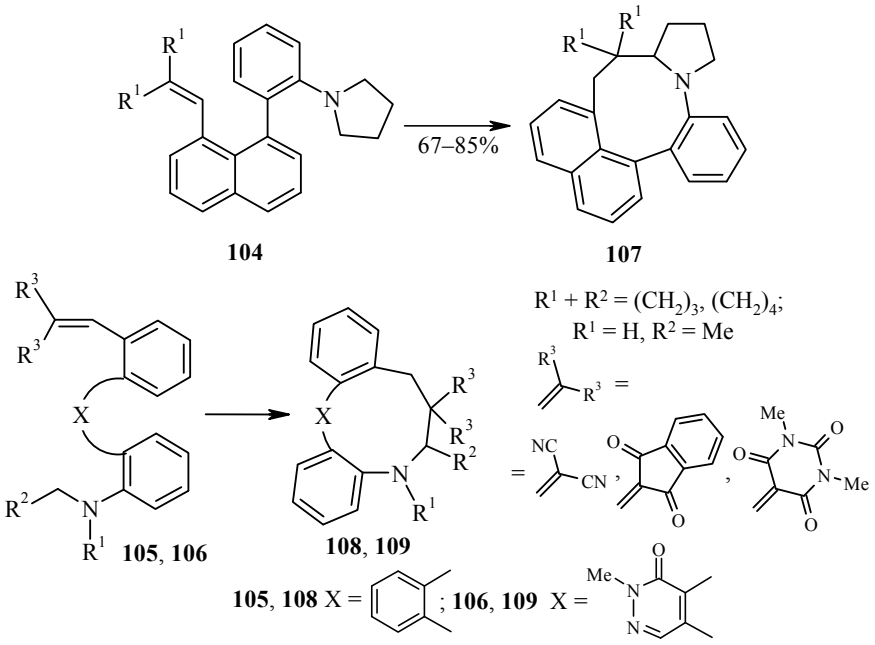


R = H, Me; R^1 = Me, Et, Ph

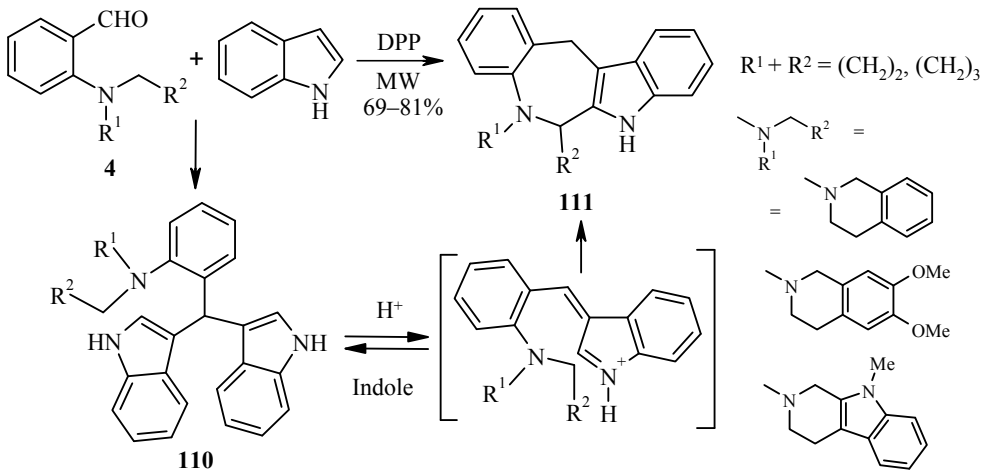
The azocines **101** and **102** were formed by cyclization of arylpyridazines **99** and biaryls **100** [79] containing a dialkylamino group and a vinyl function. In reaction with active methylene components (malonodinitrile, barbituric acids) the biarylcarbaldehyde formed not the vinyl derivatives **100**, but rather the cyclization products, phenanthridines **103**. The structure of the compounds was proven by NMR spectroscopy and X-ray structural analysis. When heated, these zwitterionic heterocycles **103** rearranged to the dibenzoazocines **102** by the *tert*-amino effect mechanism [79].



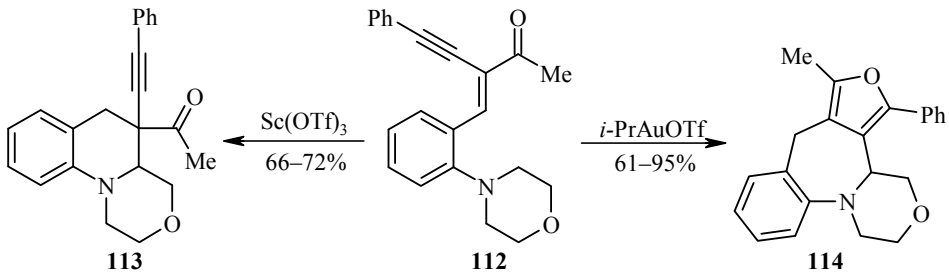
This type of cyclization was subsequently extended to 1-(*o*-dialkylaminophenyl)-8-vinylnaphthalenes **104** [80], triaryl derivatives **105**, and biarylpyridazines **106** [81]. In these cases, cyclization led to nine- and ten-membered heterocycles **107**, **108**, and **109**.



Seven-membered heterocycles were also formed in the reaction of *o*-dialkylaminobenzaldehydes **4** with indole and dimethylpyrrole [82]. With indole in the presence of acid in alcohol solution, the aminobenzaldehyde **4** usually forms the diindolylmethane **110**. Seidel and colleagues [82] showed that in the presence of *p*-toluenesulfonic acid or diphenyl phosphate (DPP) in toluene solution, cyclization occurred at the α-carbon atom of dialkylamino group, and a high yield of benzazepinoindole **111** was obtained. The authors proposed that the initially formed diindolylmethane **110** (absent at the end of the reaction) was in equilibrium with the corresponding azofulvenium ion, which underwent cyclization to the azepine **111**.

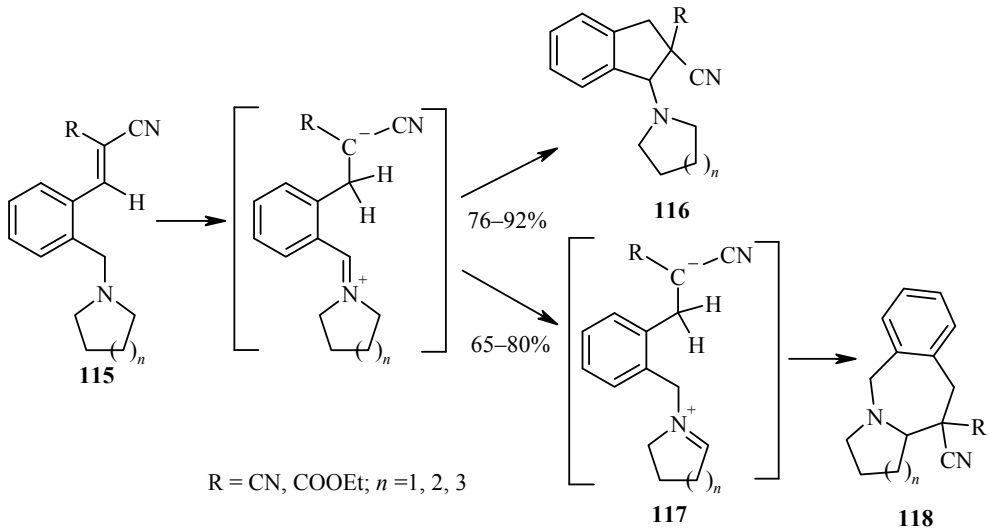


Depending on the catalyst and reaction conditions [83], the ynenone **112** underwent cyclization either to the tetrahydroquinoline **113** or to the azepine **114**.



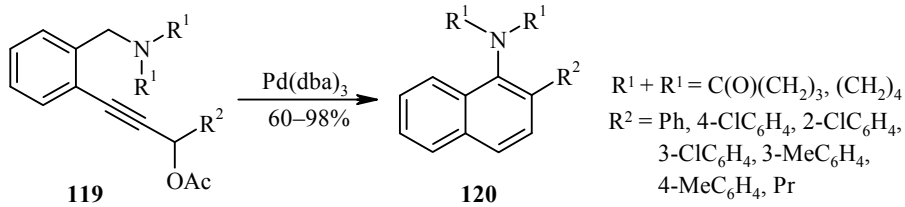
113 **112** **114**

Reactions according to the *tert*-amino effect mechanism require the presence of a conjugation chain with the nitrogen atom of the dialkylamino group. It was shown [84] that 3-[2-(pyrrolidin-1-yl)-methylphenyl]acrylonitriles **115** undewent rearrangement to the indanes **116** through a 1,4-hydride shift. At higher temperatures a 1,3-hydrogen shift also occurred with the formation of iminium ion **117**, which was transformed into the azepine **118**.



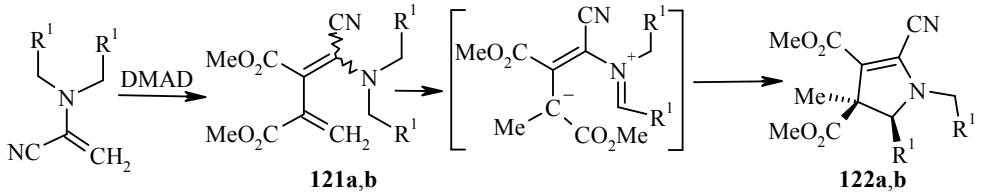
115 **117** **116** **118**

Similar reactions have been reported for the acetylenes **119**, which cyclized with the formation of naphthylamines **120** [85].



119 **120**

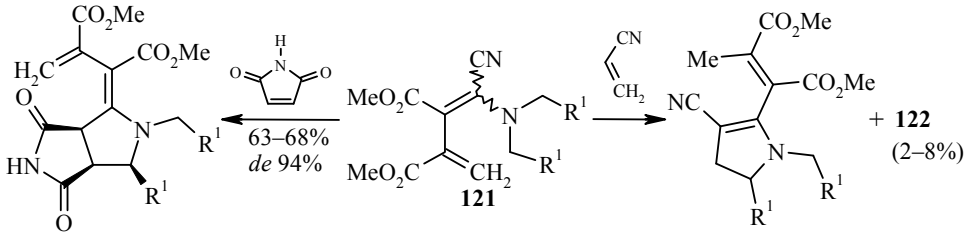
Reinhoudt reactions are also possible in linear structures. Thus, when heated in acetonitrile or DMSO, the dienamines **121a**,**b** underwent a 1,6-hydrogen shift and 1,5-electrocyclization with the formation of pyrrolines **122a**,**b** [86, 87].



121a,**b** **122a**,**b**

a $R^1 = R^2 = H$ (91%), **b** $R^1 + R^2 = (CH_2)_4$ (49%, *de* 92%)

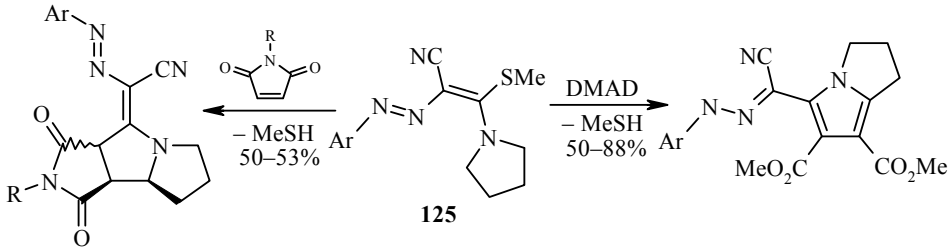
The formed intermediate dipoles **121** were shown to undergo cycloaddition with acrylonitrile or maleimide at the α-carbon atom of the amino group. After the elimination of hydrogen cyanide, the vinylpyrroles **123** or **124** were formed [87]. In addition to the cycloaddition product, small amounts of the cyclization products **122** were also isolated.



123 **121** **124** (63–91%)

$R^1 = R^2 = H$; $R^1 + R^2 = (CH_2)_4$

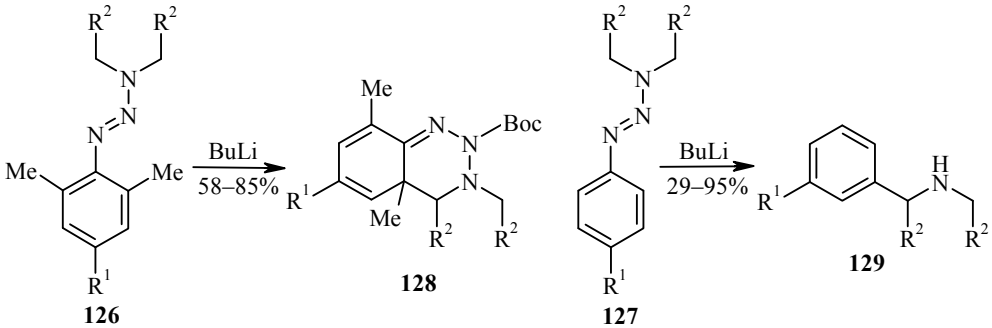
Similar cycloaddition reactions at the α-carbon atom of the amino group were demonstrated [88-90] for the azo analogs **125**. It was shown by quantum-chemical calculations [89] that the rate-limiting step was proton transfer (with 14.9 kcal/mol energy barrier).



125

R = H, Me; Ar = Ph, 4-$O_2NC_6H_4$, 2-$F_3CC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

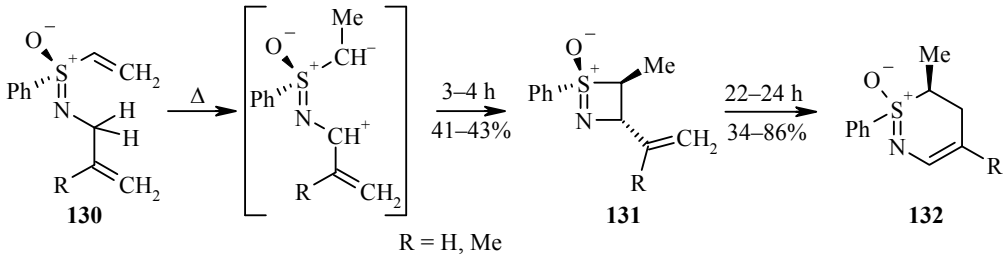
In a series of papers [91-94] it was demonstrated that *N*,*N*-dialkyl-3-aryltriazenes **126** and **127** cyclized to 1,2,3-triazines **128** when treated with butyllithium. The 1,2,3-triazines without a substituent at the *ortho* position relative to the triazene group could be transformed into the α-aryldialkylamines **129**. The key stage was an abstraction of hydrogen from the α-carbon atom of the dialkylamino group.



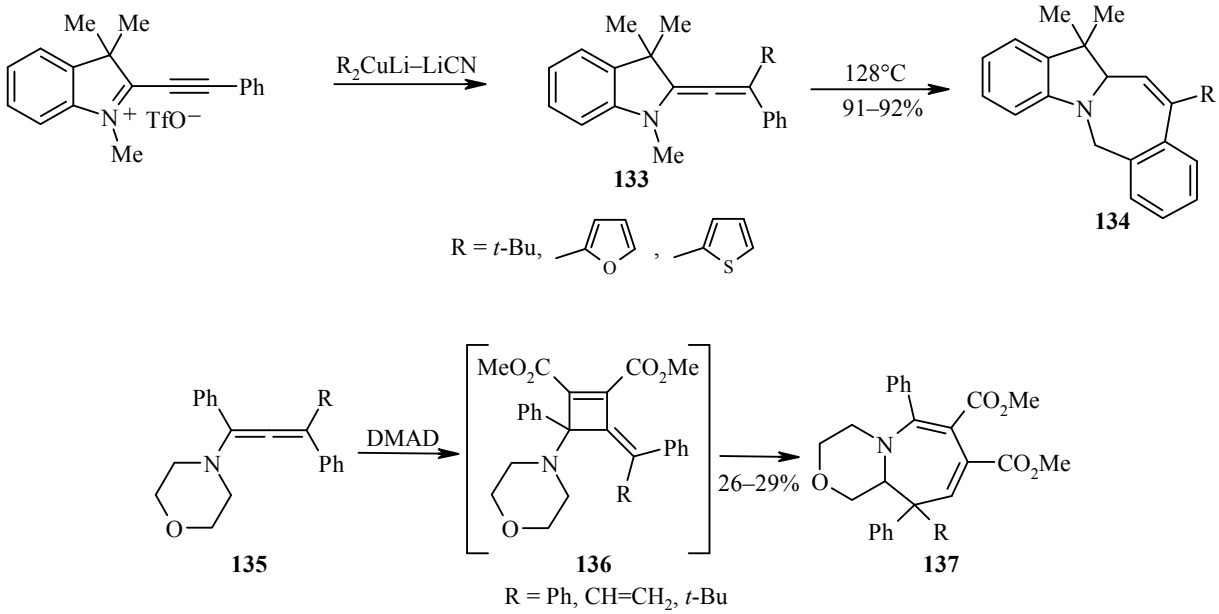
126 **128** **127** **129**

R^1 = H, Me, OMe, Cl, F; $R^2 + R^2 = (CH_2)_2$, $(CH_2)_3$, R^2 = H

It was recently discovered that *S*-alkenyl sulfoximines **130** underwent cyclization to dihydrothiazetes **131** when refluxed in toluene [95]. In the case of continued refluxing, the thiazines **132** were isolated. In contrast to the thiazete **131**, thiazines **132** were isolated as a 1:1 mixture of two diastereomers. Deuterium labeling studies by these authors indicated that the key stage was intramolecular migration of hydride ion.

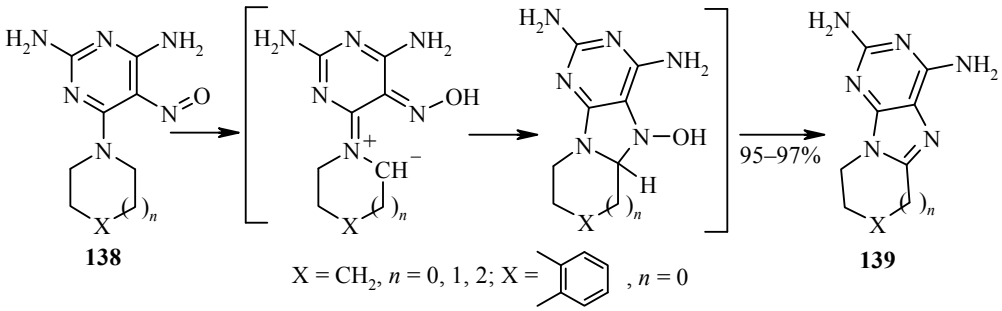


The aminoallenes **133** could also cyclize to azepines **134** when heated [96]. In the reaction of allene **135** with dimethyl acetylenedicarboxylate, the initially formed cyclobutenes **136** rearranged to the condensed rings **137**, forming a new C–C bond at the α-carbon atom of the tertiary amine [97].

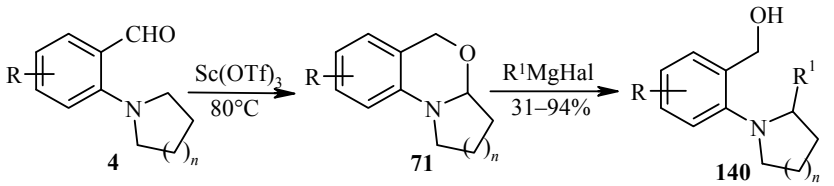


The Meth-Cohn Reaction

This type of bond formation between an α-carbon atom of dialkylamino group and a heteroatom (nitrogen, oxygen), has been reported less frequently the last decade, even though it represents an original method for the synthesis of new heterocyclic systems. Thus, it was demonstrated [98] that 6-(dialkylamino)-5-nitrosopyrimidines **138** underwent thermal cyclization to condensed purines **139**.



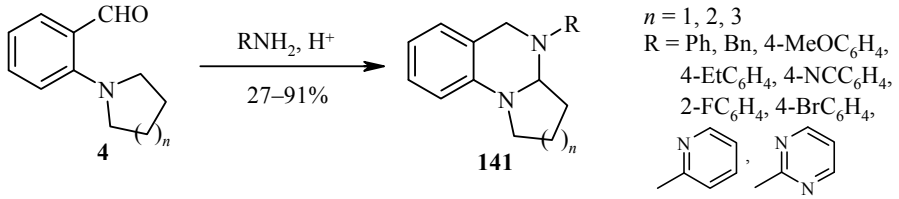
As mentioned earlier [11, 31], *ortho*-dialkylaminobenzaldehydes **4** cyclized to the benzoxazines **71** upon microwave irradiation. Trifluoroacetophenones likewise cyclized to benzoxazines upon heating [55-57]. This reaction was recently used to modify the α-position of a dialkylamino group [99]. Thus, the benzoxazines **71** formed by heating of benzaldehydes **4** in the presence of scandium triflate, were treated upon cooling with a Grignard reagent or lithium alkynyl trifluoroborate. As a result of oxazine ring opening, the functionalized hydroxymethylanilines **140** were obtained.



R = H, Cl, CF_3, NO_2, OMe; *n* = 1, 2;

R^1 = Me, *i*-Pr, Cy, $CH{=}CH_2$, *n*-C_5H_{11}, Ph, $CH_2CH{=}CH_2$, C≡CPh, C≡CBu-*t*, C≡CBu-*n*

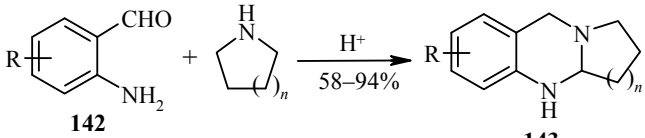
Schiff bases also undergo the Meth-Cohn reaction. Thus, in reaction with primary amines in the presence of Brønsted acids, 2-dialkylaminobenzaldehydes **4** formed the condensed benzopyrimidines **141** [100].



n = 1, 2, 3

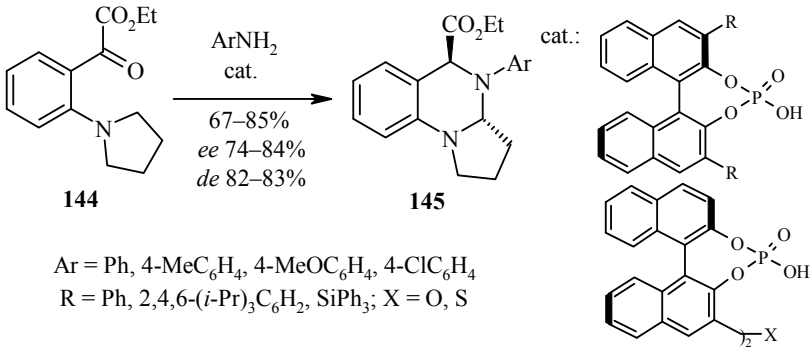
R = Ph, Bn, 4-$MeOC_6H_4$, 4-EtC_6H_4, 4-NCC_6H_4, 2-FC_6H_4, 4-BrC_6H_4,

2-Aminobenzaldehydes **142** reacted similarly with dialkylamines and formed the fused quinazolines **143** [101].



n = 1, 2, 3; R = Br, Me, Ph, CN, CO_2Et, CF_3

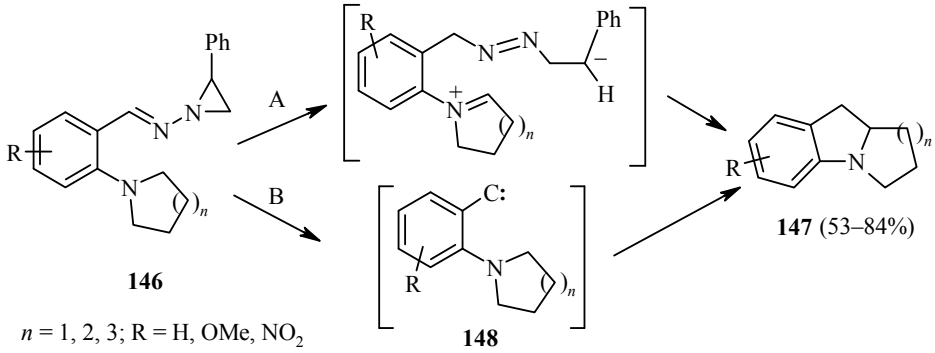
It was also shown that *ortho*-aminobenzo ketones **144** reacted with anilines in the presence of chiral Brønsted acids and formed compounds **145** with good yields and high enantioselectivity [102].



144 **145**

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4
R = Ph, 2,4,6-(i-Pr)$_3C_6H_2$, $SiPh_3$; X = O, S

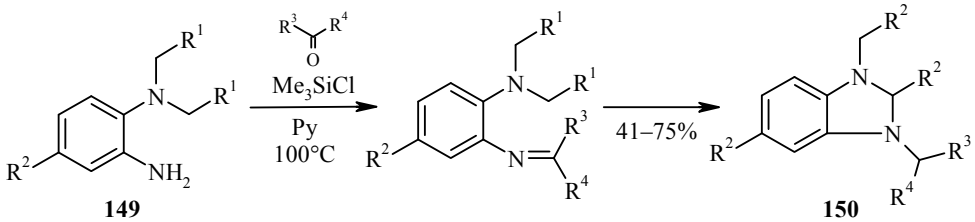
Unlike the imines, the hydrazone **146** cyclized to the indoline **147** with loss of the azo fragment and formation of a new C–C bond [103]. The authors suggested two possible mechanisms, i.e., the *tert*-amino effect (path A) and through the formation of the carbene **148** (path B).



146 **148**

n = 1, 2, 3; R = H, OMe, NO_2

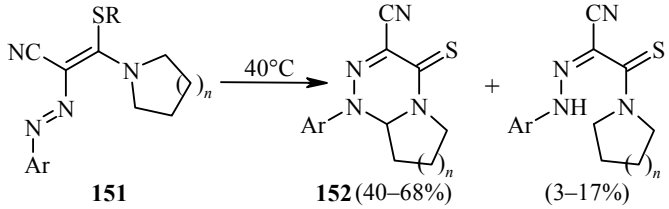
The reaction of *N*,*N*-dialkyl-*ortho*-diaminobenzene **149** [104, 105] with aldehydes and ketones in the presence of Lewis acid led to a 1,6-hydride shift and cyclization at the α-carbon atom of the dialkylamino group with the formation of a C–N bond and formation of the benzimidazole **150**.



149 **150**

$R^1 + R^1 = (CH_2)_2$, $(CH_2)_4$, R^1 = Me, Et; R^2 = SO_2Ph, SOC_6H_4Me-4, Cl, CF_3;
R^3 = H, Me; R^4 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 5-methylthiophen-2-yl

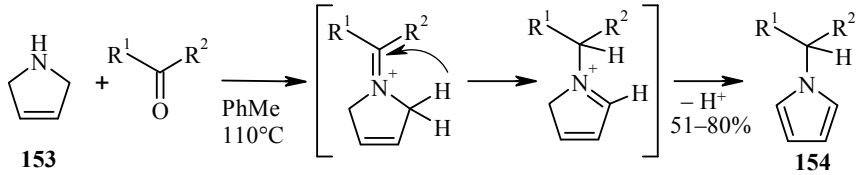
1,2-Diaza-1,3-butadienes **151**, containing allyl(propargyl)sulfanyl and cyclic dialkylamino groups, produced 1,2,4-triazines **152** by thermal cyclization [106, 107]. Furthermore, in the case of an allylsulfanyl group it was shown that propene was eliminated in this reaction [106].



151 **152** (40–68%) (3–17%)

n = 1, 2; R = $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

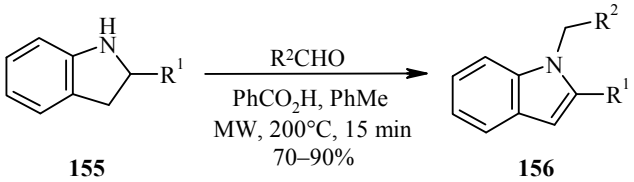
It should be noted that not all reactions involving hydrogen transfer from the α-carbon atom of a dialkylamino group result in cyclization. Examples of intramolecular oxidation–reduction (intramolecular redox processes) have been described. Thus, a reaction of the dihydropyrrole **153** with aldehydes and ketones



153 **154**

R^1 = H, Me, Et; R^2 = Ph, $CHPh_2$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-NCC_6H_4, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 4-$F_3CC_6H_4$, CHMePh, CH_2CH_2Ph

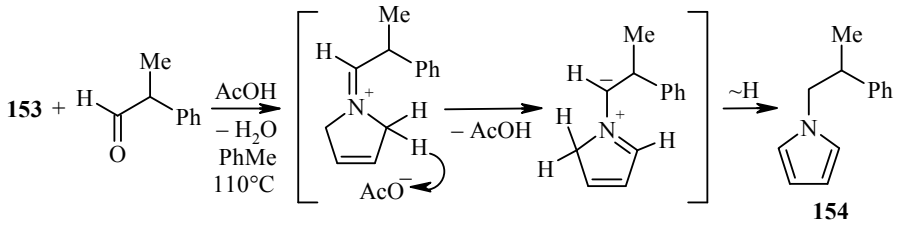
in the presence of acids led to dehydrogenation of the heterocycle and hydrogenation of the formed Schiff base resulting in the 1-substituted pyrrole **154** [108]. The reaction with indoline **155** similarly led to the indoles **156** [109, 110]. Tunge and colleagues [108] suggested that a 1,3-migration of hydrogen was the key step of this process.



155 **156**

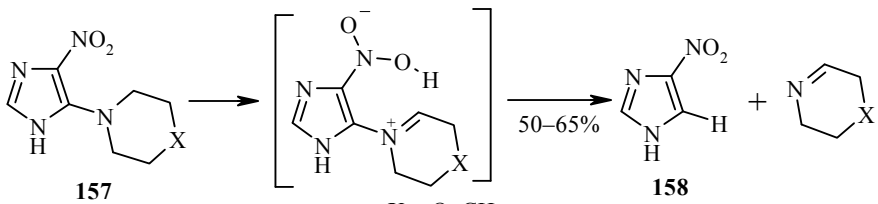
R^1 = H, Me, Ph; R^2 = Ph, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-EtC_6H_4, 4-BrC_6H_4, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 2-thienyl

On the basis of quantum-chemical calculations Chinese scientists [110] proposed that the reaction took place by an intermolecular proton transfer mechanism with an activation energy of 25.6 kcal/mol in a solvent, whereas a 1,3-migration of the proton would have a barrier of 44.6 kcal/mol.



154

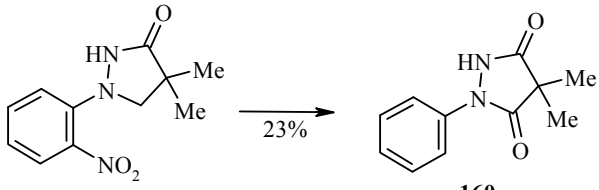
We showed [111] that a reductive elimination of dialkylamino group with the formation of nitroimidazole **158** took place when 4-(*N*,*N*-dialkylamino)-5-nitroimidazoles **157** were refluxed in butanol. A mechanism with hydride transfer to the nitro group as the key step was proposed [1, 3].



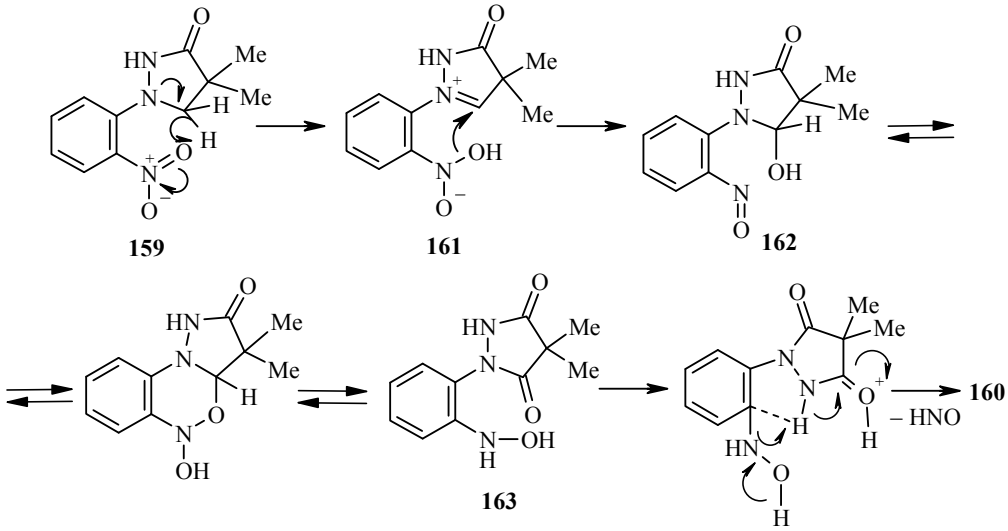
157 **158**

X = O, CH_2

Later [112] Rees showed that pyrazolidine-3,5-dione **160** was formed when the hydrazide **159** was heated in pyridine.



The authors proposed the following mechanism of denitration: The first stage involved an intramolecular hydride shift to the nitro group oxygen, and the iminium ion **161** then underwent rearrangement to the nitroso compound **162**, which was in equilibrium with the hydroxylamine **163**. Elimination of an H–N=O molecule would conclude this process.



Thus, the concept of the *tert*-amino effect includes not only cyclization but also elimination, hydrogenation–dehydrogenation, alkylation, and other reactions where the key step is hydrogen migration from the α-carbon atom of a dialkylamino group.

In conclusion we would like to point out that the Meth-Cohn and Reinhoudt reactions have previously been represented by individual uncoordinated examples, whereas in the last two decades they have evolved into a new direction of heterocyclic synthesis. The data analysed in the review allow us to expect rapid development of reactions occurring by the *tert*-amino effect mechanism in the immediate future.

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